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Signed Andrew Gussy

Dated 10 January 2000

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The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — 99-080/GB/P — 08 SEP 1999

2. Patent application number *(The Patent Office will fill in this part)* — **9921063.5**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Zeneca Limited
15 Stanhope Gate,
LONDON w1y 6ln
Great Britain

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- 8 SEP 1999
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Patents ADP number *(if you know it)*

6254007002

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

THERAPY

5. Name of your agent *(if you have one)*

DENERLEY, Paul Millington

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Global Intellectual Property, Patents
AstraZeneca PLC
Mereside, Alderley Park
Macclesfield, Cheshire, SK10 4TG
Great Britain

Patents ADP number *(if you know it)*

1030618002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

see note (a))

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Continuation sheets of this form	
Description	19
Claim(s)	
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

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Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Lynda M Slack Date 07 Sep 99

12. Name and daytime telephone number of person to contact in the United Kingdom

MRS LYNDA M SLACK - 01625 516173

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Notes

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THERAPY

The invention relates to the use of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof in treating hyperlipidaemia in mammals, particularly humans who are receiving immunosuppressive chemotherapy and to the use of the above compound or a pharmaceutically acceptable salt thereof in the manufacture of medicaments for use in such treatments.

Hypercholesterolaemia is one of the strongest risk factors for atherosclerosis which is associated with coronary artery disease (including angina pectoris, myocardial infarction and mortality), stroke (including cerebro vascular accident and transient ischaemic attack) and peripheral arterial occlusive disease. Several types of hypercholesterolaemia exist. The magnitude of hypercholesterolaemia may have consequences for the therapy, but in general, any reduction of elevated plasma cholesterol levels is generally accepted to result in an improvement of the risk profile. Dietary improvement and increased exercise are essential first steps and should continue even if drug therapy is instituted, but the therapeutic potential of drug therapy is significantly larger. Several types of drug therapy for hypercholesterolaemia are currently available. Guidelines exist for the treatment of hypercholesterolaemia for example, American Heart Association (AHA) (Anon 1988), Updated Sheffield treatment tables (Heart (1998) 80 Supp.2 S1-S29) and Recommendations of the task force of the European Society of Cardiology Guidelines (Pyorala 1994).

HMG-CoA reductase inhibitors are the most widely used prescription medication for the treatment of hypercholesterolaemia. By inhibiting the rate-controlling step in cholesterol biosynthesis, these agents effectively lower the plasma concentrations of atherogenic particles containing cholesterol such as low-density lipoprotein (LDL-C) and very low-density lipoprotein (VLDL-C). Partial inhibition of hepatic cholesterol synthesis causes up-regulation of hepatic membrane LDL-C receptors which are responsible for the clearance of LDL-C from the circulation. In addition, reduced hepatic synthesis of cholesterol is thought to result in a modest reduction in the secretion of VLDL-C particles by the liver. Clinical trials with certain HMG Co A-reductase inhibitors, such as in the Scandinavian Simvastatin Survival Study, confirm a reduction in cardiovascular morbidity and mortality with such agents, and

may even promote regression of atherosclerotic vascular lesions. Various HMG Co A-reductase inhibitors are marketed, and are collectively referred to as 'statins'.

Despite the impressive benefits of statin therapy, less than optimal therapeutic results may be achieved in some subjects, particularly in the more severe classes of hypercholesterolaemia. This can be due to the occurrence of reversible increases in liver transaminase levels at higher dose levels of statins as well as differences in efficacy between different statins. Clinically important (>3 times upper limit of normal [ULN]) elevations in serum alanine aminotransferase [ALT]) have been reported for atorvastatin in 0.8 per cent of patients at low doses of atorvastatin and higher at raised doses (European Summary of Product Characteristics [SmPC] for atorvastatin [Lipitor™]). In all cases the effect is dose-related and reversible. In general it is the incidence of ALT increases which limits dose escalation of statins rather than a limit to further increases in efficacy.

The first generation statins (such as lovastatin, pravastatin and simvastatin - prodrug derivatives of fungal metabolites, and fluvastatin) are categorised in that they achieve only a limited cholesterol lowering affect before the dose administered is limited by elevations in serum ALT. Second generation "superstatins" (such as atorvastatin - synthetic compounds-structurally distinct from first generation compounds) inhibitors are categorised in that they lower cholesterol levels to a much higher degree than the earlier first generation of statins before their dose is limited by serum ALT levels. Atorvastatin has been successful over the first generation of statins. Since its launch in the USA atorvastatin has reached sales in 1998, doubling from 1997, of $2.2 billion, capturing 38% of new prescriptions for cholesterol-lowering agents in the US now the most widely prescribed hypolipidaemic agent in the US (Warner-Lambert 1998 annual results).

An additional adverse event, reported for statins in general, is myopathy, defined as symptoms of muscle pain, tenderness and weakness, with creatinine kinase (CK) values >10 x Upper Limit of Normal (ULN). This adverse event is not considered to be dose related, and in addition the adverse events are potentially more serious, and consequently more problematical, especially in patients receiving transplants, as discussed below. In severe cases this can lead to rhabdomyolysis, which is a rare life threatening condition sometimes associated with renal failure. The incidence of raised CK levels (>10 x ULN is the clinically signicant level - on 2 occasions at least 1 week apart with symptoms = myositis according to

FDA) for statins has been reported as 3.1 per cent. (SmPC for atorvastatin). Myopathy and rhabdomyolysis have been particularly associated with taking a statin in combination with gemfibrozil, niacin, cyclosporin or erythromycin, (Hunninghake H. Et al. Current Opinion in Lipidolgy (1992), 3, 22-28) which are all substrates for P450 3A4. The increase in adverse events associated with taking a combination of a statin drug with one of the other drugs mentioned above is probably due to a drug:drug interaction likely related to the metabolism of most statins by cytochrome P450 3A4. Therefore when a drug which is also metabolised by P450 3A4 is administered alongside a statin which also is metabolised by P450 3A4, interactions are more likely to occur, such as muscle damage which are possibly due to elevated statin levels in muscle cells inhibiting farnesylation and geranylgeranylation of muscle protiens . Therefore, currently on the labels of all commercially available statins combination with certain drugs that are metabolised by P450 3A4 is not recommended and is contraindicated in certain cases. Nearly all drugs are metabolised to some degree in the human, generally to a less lipid soluble compound which is more easily excreted by the kidney. Many of the drug metabolic enzymes are found in the endoplasmic reticulum (which form microsomes upon homogenisation) of hepatocytes. The liver is the major site of drug metabolism because the liver cells (hepatocytes) contain particularly high concentrations of drug metabolising enzymes. Cytochrome P450 is a family of isoenzymes found in hepatic microsomes. Six specific P450 isoenzymes are responsible for the metabolism of most of the commonly used drugs, namely P450 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4.

A major disadvantage of the currently available "super statin" , atorvastatin, is that atorvastatin is metabolised by cytochrome P450 enzymes in particular 3A4, which may cause drug interactions with other drugs which are inducers, inhibitors or substrates of the same P450 enzyme which metabolises atorvastatin. All of the first generation of statins are metabolised by P450 also. However, the rate of metabolism of pravastatin is sufficiently low that it is considered less susceptible to clinically relevant drug interactions. Therefore despite the lower efficacy of pravastatin , in its currently available doses , at reducing hypercholesterolaemia this is currently the statin of choice in combination with other drugs where the possibility of drug interactions is unacceptably high, such as with immunosuppressive chemotherapy, particularly in transplant patients.

(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-

[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof (the calcium salt of which is disclosed in Figure 1 below), hereinafter referred to as the Agent, is also a statin and belongs to the class of what is now starting to be called a "superstatin".

The Agent is disclosed in European Patent Application, Publication No. 0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444 as an inhibitor of HMG-CoA reductase which is a major rate-limiting enzyme in cholesterol biosynthesis. The Agent is taught as useful in the treatment of hypercholesterolaemia, hyperlipoproteinaemia and atherosclerosis.

The Agent is not metabolised by cytochrome P450 3A4 and therefore does not possess the same potential for drug interaction shared with the currently available "super statin", i.e. atorvastatin, or any of the other currently available statins.

Two common drugs used in suppressing the human immune system, cyclosporin and tacrolimus (formerly called FK506), are known to be metabolised by cytochrome P450 3A4. In particular cyclosporin is also a known inhibitor of P450 3A4 and is therefore likely to reduce the metabolism of any other drug which is metabolised by P450 3A4.

Therefore where immunosuppressive therapy is prescribed, such as with the drugs cyclosporin and tacrolimus (especially cyclosporin), the attendant physician must be cautious as to any other therapy which may be jointly presented to the patient in combination. Immunosuppressive therapy is most commonly used before, during and after human transplant operations. In particular with cardiac transplants the attendant physician may wish to also place the patient on statin therapy to reduce future incidents of coronary heart disease, stroke, peripheral arterial occlusive disease or peripheral vascular disease, particularly in patients with elevated cholesterol or in normolipidaemic patients with other risk factors associated with heart disease. In particular, within this special patient group (human transplants), these patients are at high risk of developing atherosclerosis in the transplant organ in an aggressive fashion and within a short period of time due in part to the surgical damage to the blood vessels during transplantation and previously underlying untreated conditions. Hyperlipidemia is common after transplantation even in patients who did not suffer hyperlipidemia prior to transplantation, incidence 60-80% of recipients. It is known that certain immunosuppresive drugs, such as steroids, cyclosporin and tacrolimus, raise

cholesterol levels in patients (Wierzbicki AS (1999) IJCP 53 (1) 54-59). In addition cyclosporin and tacrolimus may raise the levels of fibrinogen and lipoprotein (a) in the patient, further accelerating the progression of atherosclerosis in the transplant patient (Hohaye H, Clin.Transplant (1997) 11, 225-230 and Hilbrands LB, J.Am.Soc.Nephrol (1995) 5, 2073-2081). This unusually accelerated atherosclerosis is present in about 20% of heart transplant patients at 1 year and 40-65% at 5 years (Chang G. Et al. American Heart Journal (1998), 136(2), 329-334). The incidence of accelerated atherosclerosis has been reported as causing a 1-18% incidence of CHD at one year and 20-50% at 3 years in cardiac transplant patients (Erdoes LS, J.Vasc.Surg. (1995) 22, 434-440). Lovastatin, pravastatin and simvastatin have all shown to lower cholesterol levels in heart transplant patients. In a placebo controlled study pravastatin increased survival of transplant patients by 1 year and reduced the incidence of hemodynamic organ rejection significantly. Because of the lower incidence of serious drug interaction with the immunosuppresive therapy pravastatin is currently the statin of choice in post transplant treatment regimes. However, as discussed above pravastatin does not lower lipid/cholesterol levels to such a great extent as, for example, atorvastatin.

We have discovered that the Agent is extremely effective at treating hypercholesterolaemia in patients following cardiac transplantation and that the Agent is not metabolised by cytochrome P450 enzymes. Therefore we have found through the use of the Agent in a clinical study that the Agent may be conveniently dosed to patients who are undertaking immunosuppressive therapy without any clinically significant side effects associated with the concomitant dosing of the Agent and the immunosuppressive drug(s) and, in addition also achieve much higher levels of cholesterol lowering than has previously been achieved, such as by the use of pravastatin.

We present as the first feature of the invention a method of providing safe non-interacting cholesterol lowering therapy to a mammal, including a human patient, undertaking immunosuppressive chemotherapy which method comprises administering to the patient the Agent.

Particular patients undertaking immunosuppressive chemotherapy who may benefit from the method of the invention are those who:

1) suffer primary (type IIa) hypercholesterolaemia (LDL-L $\geq$ 135 and TG<200);

2) suffer combined (type IIb) hypercholesterolaemia (LDL-C≥ 135 and TG≥200);

3) patients with established CHD or other atherosclerotic disease, such a PVD, stroke or peripheral arterial occlusive disease;

4) patients who are at high risk of developing CHD or other atherosclerotic disease, such as described above, because of a combination of risk factors. The term "high risk" is defined in the "Recommendations of Second Joint Task Force of European and other Societies on Coronary Prevention", (Wood, D. et. al. European Heart Journal, Atherosclerosis and Journal of Hypertension 1998) as absolute CHD risk of ≥ 20% over 10 years or will exceed 20% if projected to age 60 years. Whether a patient is at high risk or not may be determined by the charts which accompany the above recommendations and which charts are incorporated herein by reference. For example, a male patient in his 40s who smokes and has a systolic blood pressure of 180 mm Hg or higher and a total plasma cholesterol concentration of 7 mmol/L or higher will be classified as high risk. Similarly other guidelines for reducing risk factors may be applied such as those described in;

a) JAMA, June 16, 1993-Vol 629, No.23, Pages 3015-3023 - "Summary of the NCEP Adult Treatment Panel II Report - specifically Figure 1. Page 3018-3019 which is incorporated herein by reference.

b) Post Graduate Medical Journal 1993; 69(811): 359-369 - "Management of hyperlipidaemia: guidelines of the British Hyperlipidaemic Association"- specifically Table V and Table VI are incorporated herein by reference.

c) Heart 1998; 80 Supplement 2:S1-S29 - "Joint British recommendations on prevention of coronary heart disease in clinical practice"- specifically Figure 1 on pages S4-S5.

d) The Lancet 1995; December 2, Vol.346, 1467-1471 - "Sheffield risk and treatment table for cholesterol lowering for primary prevention of coronary heart

disease" - specifically the Table appearing at page 1468 is incorporated herein by reference.

5) patients who suffer type I or II diabetes;

6) patients who are about to or have already undertaken a heart transplant;

The statin therapy may be administered so as to achieve in the patient undertaking immunosuppressive chemotherapy.

1) a reduction in the internal thickness of coronary artery atheroma of $\geq 30\%$ as measured by IVUS;

2) a reduction of LDL-C of at least 30, 40, 50%

3) a maintenance or increase of HDL-C of at least 5, 10, 15%

4) a change in any of the above values better than pravastatin at a similar dose and over the same period.

As a further feature of the invention and due also to the fact that the Agent is not metabolised to any significant extent by P450 isoenzymes it is possible to administer, more safely than before, to a patient receiving immunosuppresive therapy a fibrate and the Agent. As discussed earlier the administration of a fibrate and a statin has previously been associated with a higher incidence of rhabdomyolysis and myopathy. In addition fibrate drugs do interact with cyclosporin due to both being metabolised by the same P450 isoenzyme. Therefore, the use of a statin and a fibrate drug in combination with immunosuppresive therapy was previously contraindicated due to the likelihood of possible serious interactions (Hunninghake 1992, Wanner C. Kidney Int. (1995) 52(suppl.), S60-S62 and Katznelson S. Contributions Nephrol. (1997) 120, 97-104). However, if possible, it would be advantageous to also administer a fibrate alongside a statin since fibrates are known to lower different lipoproteins

than statins and therefore their combined pharmacology would be complementary in reducing even further the likelihood of CHD and other diseases mentioned above associated with the formation of atherosclerosis. Therefore the possibility of combining the Agent, which is not metabolised by P450 3A4, with a fibrate and an immunosuppresive therapy offers the additional possibility of lowering cholesterol to a greater extent in such patients than previously acheved and more safely than could previously be achieved by the administration of a statin, a fibrate and an immunosuppresive drug.

Fibrate drugs are thought to act through peroxisomal proliferating activator receptor-α (PPAR-α) and affect gene activation at a number of genes involved in atheroma. Patients on fibrate drugs show improved LDL subfraction distribution (reduced VLDL and raised HDL), reduced LDL and reduced triglyceride levels, and possible advantages through improving insulin sensitivity. Examples of fibrate drugs include, bezafibrate, ciprofibrate, fenofibrate and gemfibrozol.

By use of the term "safe non-interacting statin therapy" we mean that the Agent is not metabolised by P450 3A4 and therefore does not affect the metabolism of the immunosuppresive therapy or *vice versa*.

Diseases and conditions in which immunosuppressive therapy may be prescribed include, in addition to organ transplantation mentioned above, autoimmune diseases, including rheumatic disorders, such as, rheumatoid arthritis, osteoarthritis, lupus erthematosus; and other autoimmune disorders such as idiopathic thrombocytopenic purpura, autoimmune haemolytic anaemia and acute glomerulonephritis.

The agent may be administered at the same time as the immunosuppressive chemotherapy, or if not at the same time within a short time period of administration of the immunosuppressive therapy, such as in the same day, within 6, 3, 2 or 1 hour.

The Agent may be administered according to the cholesterol-lowering effect desired from a range of 5-80 mg per day in any number of unit dosages, preferable once a day dosing. Ideal doses are 10, 20 and 40 mg once per day. Preferred doses are 20 and 40mg once per day.

The dosage regimen administered to the patient is at the discretion of the attendant physician. Factors the physician may need to consider in deciding the most suitable dose for a patient are; the sex, age, weight, route of administration and medical condition of the patient. Preferred oral doses of the Agent are from 1 to 200 mg/day, preferably 5 to 80 mg/day, and

more preferably 5 to 20 mg/day. Oral dosage may be administered in the following unit dosage forms, or multiples thereof, to achieve the total daily dose, 5, 10, 20, 40 or 80 mg. Oral pharmaceutical formulations may be presented in the form of a tablet, caplet, capsule, granule, powder, elixir or such like and may be prepared by art recognised techniques of intimately mixing the Agent and excipient(s). Illustrative examples of suitable formulations are provided hereinbelow.

Particular immunosuppressive drugs which may be combined with the Agents are those which are metabolised by liver enzymes and therefore are not likely to have a drug interaction with the Agent as a result of the Agent or immunosuppressive drug affecting the metabolism of the other by modulating in any way an enzyme responsible for the metabolism of either the Agent of immunosuppressive drug. Examples include those described above as well as corticosteroids, which are metabolised in the liver. Examples of corticosteroids include prednisone (especially used for organ transplantation). Preferably at least one of the immunosuppressive agents, if more than one agent is used, is either cyclosporin or tacrolimus, preferably cyclosporin.

ABBREVIATIONS AND CONVENTIONS USED HEREIN

Term	Abbreviation
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CABG	Coronary artery bypass graft
CHD	Coronary heart disease
CHF	Congestive heart failure
Cmax	Maximum concentration
Cmin	Minimum concentration
CK	Creatine kinase
CK-MB	Creatine kinase (MB Band)
CVA	Cerebrovascular accident

Term	Abbreviation
EAS	European Atherosclerosis Society
γGT	Gamma-glutaryl-transferase
HDL	High-density-lipoprotein
HMG CoA	3-hydroxy-3-methylglutaryl Coenzyme A
HRT	Hormone replacement therapy
IU	International units
IVUS	Intravascular ultrasonography
LDL	Low-density lipoprotein
LDL-C	Low-density-lipoprotein-cholesterol
mmHG	Millimeters of mercury
NCEP	National Cholesterol Education Program
NDSR	Nutrition Data System for Research
PFA	Polyunsaturated fatty acids
SFA	Saturated fatty acids
$t_{1/2}$	Half-life
T_4	Thyroxine
TC	Total cholesterol
TG	Triglycerides
TIA	Transient ischemic attack
t_{max}	Time to reach maximum concentration
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VLDL	Very low-density lipoprotein

The following non-limiting example is of a clinical trial to demonstrate the performance of the invention.

PROTOCOL

Title: A Double-blind, Parallel Group Study to Assess the Change in Coronary Artery Atheroma Burden Post Cardiac Transplantation as Measured via IVUS after 12 Months Dosing with the Agent versus Pravastatin

Objectives: The primary objective of the study is to measure change in maximal mean intimal thickness of the anterior descending coronary artery as assessed by intravascular ultrasonography (IVUS) (read centrally) after 12 months of treatment with the Agent or pravastatin. A change from baseline of ≥30% in intimal thickness will be considered clinically significant.

The secondary objectives of the study are to measure the effects on coronary artery atheroma burden and to compare effects of the Agent with the following assessments:

- evidence of rejection as assessed by adverse event reports.
- measurement of LDL-C, HDL-C, apoB, apoA-I, Lp (a) concentrations, ex vivo platelet aggregation, fibrinogen, PAI-I, and the concentrations of circulating markers of vascular inflammation.
- comparison of lipid values after 52 weeks of treatment.
- measurement of inflammatory markers after 52 weeks of treatment (HLA antigen VCAM/ICAM expression as assessed by biopsy).
- to determine the drug's safety and tolerability.

Type and number of subjects: Approximately 40 men and women (aged 18 years and older) post cardiac transplant with hypercholesterolemia and triglycerides <400 mg/dl at the time of randomisation.

Trial treatment: Once daily doses of the Agent (10 mg) or pravastatin (10 mg) for two weeks, then titration of dose to 20 mg of the Agent or pravastatin 20 mg. After 4 weeks the dose should be titrated up to 40 mg of the Agent or 40 mg pravastatin. Patients who have had their dose titrated up to 40 mg may have their dose titrated down to 20 mg, at the discretion of the investigator.

Duration of treatment: Eligible subjects randomised to 1 of 2 treatment groups, the Agent or pravastatin, for 52 weeks.

Primary measure: Mean change from baseline in maximal mean intimal thickness, as assessed by IVUS (read centrally).

Secondary measures: Percent change from baseline in LDL-C at 6 and 12 months.

Percent change from baseline in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, and triglycerides (TG).

Percent change from baseline in ApoB, ApoB/ApoA-1, ApoA-1, Lp (a), and particle subfractions at 6 and 12 months.

Percentage of subjects on each of the possible titrated doses at 12 months.

Endocardial rejection will be considered an adverse event.

Percent change from baseline in inflammatory markers (HLA antigen level and ICAM/VCAM expression).

Safety evaluation as determined by adverse events, physical examination, and laboratory data.

TRIAL DESIGN

This is a multicenter, randomized, double-blind, parallel-group clinical trial. Within 1 to 4 weeks post surgery, subjects are randomized to receive either the Agent or pravastatin for 52 weeks. Subjects start treatment at a dose of 10 mg of either the Agent or pravastatin at Visit 2 and the dose is titrated to 20 mg at Visit 3 during the forced titration period. At Visit 4 and subsequent visits, the investigator has the option to increase each drug up to 40 mg during the optional titration period. Patients who have had their dose titrated up to 40 mg may have their dose titrated back down to 20 mg at the investigator's discretion.

TRIAL DESIGN

	Pre-transplant	Forced Titration		Optional Titration						
Visit	1	2	3	4	5	6	7	8	9	10	11
Week (W)/ Month (M)		W0	W2	W4	M2	M3	M4	M5	M6	M9	M12
Agent (mg)		10	20	≥ 20*							
PRAVASTATIN (mg)		10	20	≥ 20*							
		Randomisation**									

* Subjects who are tolerating 20 mg of the Agent or Pravastatin at Visit 4 may have their dose titrated up to 40 mg, at the discretion of the investigator.

** Subjects should be randomized within 4 weeks of cardiac transplantation and must not have received any other lipid lowering therapy post-surgery.

Inclusion criteria

(1) have undergone cardiac transplantation up to four weeks prior to randomization

(2) fasting TG concentrations of <4.52 mmol/L (400 mg/dl)

Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the trial:

(1) Use of other cholesterol lowering drugs or lipid lowering dietary supplements or food additives post-transplantation prior to entering the study.

(2) history of serious or hypersensitivity reactions to other HMG-CoA reductase inhibitors

(3) pregnant women, women who are breast feeding, and women of child bearing potential who are not using chemical or mechanical contraception or have positive serum pregnancy test (a serum β-Human chorionic gonadotropin [β-HCG] analysis)

(4) Subjects with a history of diabetic ketoacidosis within the past 5 years are excluded.

(5) uncontrolled hypothyroidism defined as a thyroid stimulating hormone (TSH) >1.5 times the ULN at Visit 2 or subjects whose thyroid replacement therapy was initiated within the last three months

(6) use of concomitant medications as detailed below - except immune suppressants and diazepam.

(7) current alcohol and/or drug abuse

(8) active liver disease or hepatic dysfunction as defined by elevations of ≥ 1.5 times the ULN at Visit 2 in any of the following liver function tests: ALT, AST, or bilirubin

(9) serum CK > 3 times ULN at Visit 2

(10) serum creatinine > 220 μmol/L (2.5 mg/dl)

(11) subjects with cancer or with a history of cancer who, in the opinion of the investigator, have more than a minimal chance of recurrence.

(12) participation in another investigational drug trial less than 4 weeks before randomization into the trial

(13) subjects randomized to double-blind treatment who subsequently withdrew cannot re-enter this trial

(14) serious or unstable medical or psychological conditions that, in the opinion of the investigator, would compromise the subject's safety or successful participation in the trial

(15) subjects taking cyclic hormone replacement therapy (HRT), cyclic oral contraceptive therapy (OCT), a depot progesterone injection, or subjects whose non-cyclic HRT or OCT was initiated within the last 3 months

DISALLOWED MEDICATIONS

CLASS OF DRUG	GENERIC NAME
Antibiotics/ antifungals	Erythromycin Base Erythromycin Ethyl Succinate, Acetyl Sulfisoxazole Rifampicin Fluconazole Ketaconazole Itraconzole
Anti-epileptics/ antidepressants	Phenytoin Phenobarbitol Fluoxetine Carbemazepine
Acne treatment	Isotretinoin
Antiulcer drugs	Cimetidine Cisapride

CLASS OF DRUG	GENERIC NAME
Systemic Steroids	Triamcinolone Acetonide Triamcinolone Diacetate Betamethasone Sodium Phosphate Betamethasone Acetate Hydrocortisone Hydrocortisone Acetate Hydrocortisone Sodium Phosphate Hydrocortisone Sodium Succinate Cortisone Acetate Dexamethasone Dexamethasone Acetate Dexamethasone Sodium Prednisone Methylprednisolone Methylprenisolone Acetate Methylprednisolone Sodium Succinate Prednisolone Tebutate Prednisolone Sodium Phosphate Methyltestosterone Fluoxymesterone
Antihistamine	Astemizole Terfenadine

CLASS OF DRUG	GENERIC NAME
Lipid Regulation	Niacin/Nicotinic Acid Probucol Psyllium Preparations Clofibrate Cholestyramine Colestipol Hydrochloride Gemfibrozil Atorvastatin Lovastatin Pravastatin (except study medication) Simvastatin (except study medication) Fluvastatin Cerevestatin Fish oils (any dose) lipid lowering dietary supplements lipid lowering food additives
Hormone Therapy	Estrogen and progesterone combinations which are bi or tri phasic.

Friedewald Equation

The LDL-C level is calculated from the Friedewald equation as follows:

For SI units (mmol/l)

LDL-C = Total cholesterol - [HDL-C + Triglycerides/2.2)

For non-SI units (mg/dl):

LDL-C = Total cholesterol - [HDL-C + triglycerides/5]

Summary of NCEP Goals for Lipid Management[a]

NCEP Risk Category	Target LDL-C (NCEP)
No CHD/PVD and 1 or no risk factors	< 160 mg/dL
No CHD/PVD and 2 or more risk factors	< 130 mg/dL
Clinically evident CHD/PVD	≤ 100 mg/dL

5 [a] Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Bethesda (MD): National Institutes of Health, National Heart and Lung Institute 1993 Sep Report No.: 93-3095.
NCEP National Cholesterol Education Program.

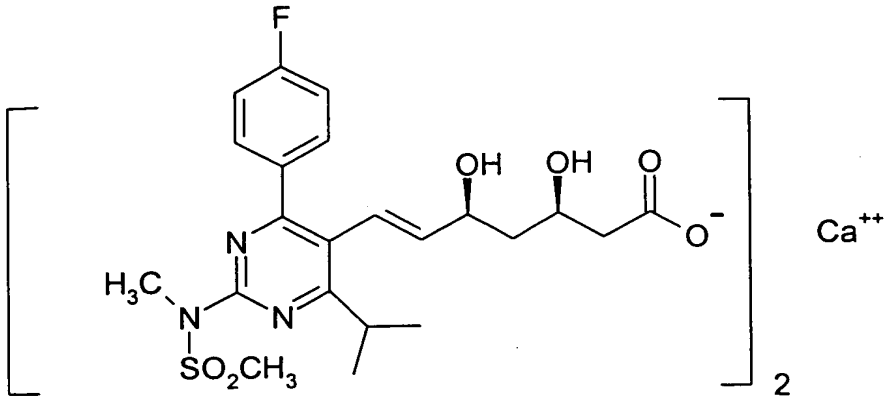

Fig.1